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European Code against Cancer 4th Edition: Alcohol drinking and cancer☆

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ABSTRACT

Alcohol consumption is the third leading risk factor for disease and mortality in Europe. The International Agency for Research on Cancer (IARC) Monographs provide strengthened evidence that the consumption of alcoholic beverages is causally associated with cancers of the oral cavity, pharynx, larynx, oesophagus, liver, colorectum and female breast, even for low and moderate alcohol intakes. The risk of cancer increases in a dose-dependent manner, and the higher the amount of alcohol consumed, the higher the risk of developing cancer. Several biological mechanisms explain the carcinogenicity of alcohol; among them, ethanol and its genotoxic metabolite acetaldehyde play a major role. Taking all this evidence into account, a recommendation of the 4th edition of the European Code against Cancer (ECAC) is: "If you drink alcohol of any type, limit your intake. Not drinking alcohol is better for cancer prevention."

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1. Introduction

Alcohol consumption is linked to a large number of health impairments, chronic diseases and deaths worldwide [1]. The 2012 Monograph of the International Agency for Research on Cancer (IARC) provides stronger evidence on the carcinogenicity of alcohol by tumour sites and by mechanisms of alcohol carcinogenesis even for low and moderate alcohol intakes [2,3]. The IARC Monographs reached the conclusion: "alcohol consumption is carcinogenic to humans (Group 1); ethanol in alcoholic beverages is carcinogenic to humans (Group 1); acetaldehyde associated with the consumption of alcoholic beverages is carcinogenic to humans (Group 1)" [2]. Overall, there is no consistent difference in cancer risk between different types of alcoholic beverage [4–6]. Europe is the region of highest alcohol consumption in the world, with an average consumption of more than twice the global average; it has

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Abbreviations: IARC, International Agency for Research on Cancer; EU, European Union; RR, relative risk; UADT, upper aero digestive tract; ADH, alcohol dehydrogenase; ALDH, acetaldehyde dehydrogenase; MTHFR, methylenetetrahydrofolate reductase; ER, estrogen receptor; PR, progesterone receptor; WHO, World Health Organization.

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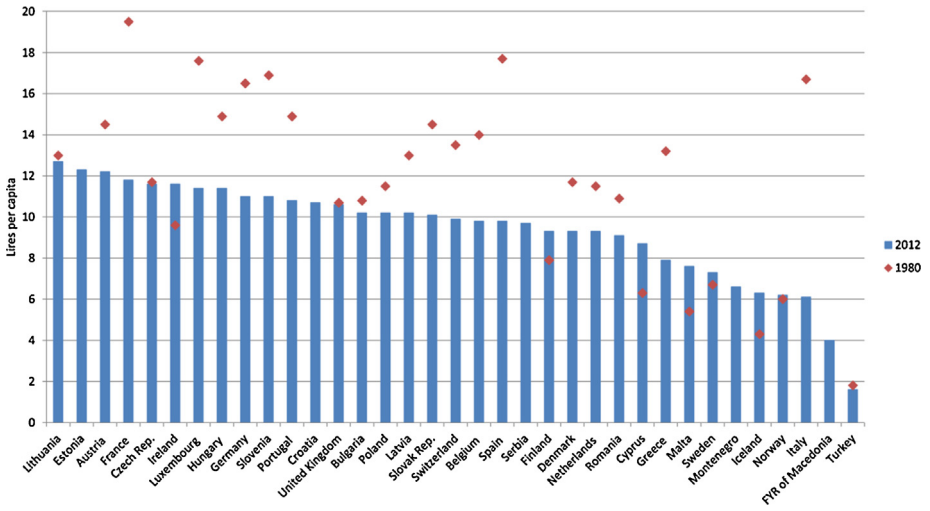

Fig. 1. Average European adult alcohol consumption in litres/capita/year among populations aged ≥15 years (years 2010 and 1980). From calculations provided by the OECD based on "Health at a glance: Europe 2012. OECD Publishing, 2012" [8].

a high prevalence of hazardous drinkers and an average alcohol-attributable cancer burden which also exceeds by far the global average [1]. Taken together, the 4th edition of the European Code Against Cancer (ECAC) [7] advocates action-oriented recommendations for the general public. The ECAC recommends decreasing or cutting alcohol consumption in order to prevent several types of cancer and to improve overall health.

1.1. European alcohol consumption among adult and young generations

Per capita alcohol consumption has been falling in the European Union (EU) as a whole over the past three decades, while remaining particularly high compared to the global average. The most recent sales data show that individuals aged ≥15 years drink on average 10.7 l of pure alcohol per year [8]. Consumption tends to be higher in the Central-Eastern and Eastern countries such as, for example, Latvia, Romania, Lithuania and Austria, all of which have an average consumption >12 l per capita. At the other end of the spectrum, Mediterranean countries (e.g., Italy, Malta and Greece) and Nordic Countries (e.g., Norway, Sweden and Iceland) have relatively lower levels of consumption, in the region of 7–8 l of pure alcohol per adult person (Fig. 1). Gender, age and socio-economic status are key factors in determining levels of alcohol consumption [9]. Men are more likely to consume alcohol than women, and to drink more when they do [10], particularly in Central, Western and Northern EU countries. Compared to older adults, young and middle-aged people tend to drink higher volumes of alcohol [11]. Women with higher level of education tend to drink more alcohol while the opposite is generally true for men [10]. Hazardous drinking behaviours, such as binge drinking (i.e., the occasional consumption of ≥60 g of pure alcohol on the same occasion and at least one day in the last month), have been increasing over the past 20 years [13], especially in Germany and Ireland and among younger generations [14–17]. The prevalence of binge drinkers doubled in France and has increased by about 30% in Germany between 2002 and 2008 [13]; binge drinking was reported by 36% of girls and 40% of boys in 2010 [8].

1.2. Effect of alcohol drinking on coronary heart disease

Light to moderate alcohol consumption might be associated with a reduced risk of coronary heart disease. A small reduction in risk has been suggested for the consumption of one drink every second day (not including as 'abstainers' those who reduced or stopped drinking [18]), and is probably confined to middle-aged or older individuals [18–20]. Similarly, a recent systematic review suggests that light to moderate alcohol consumption might be associated with a reduced risk of cardiovascular outcome, in particular coronary heart disease mortality compared to stroke [21], but again reverse causation and residual confounding cannot be excluded. While there is some evidence that low doses of alcohol may raise blood levels of high-density lipoprotein and improve reduction in coagulation [22,23], high doses may precipitate cardiac arrhythmias, myocardial ischaemia or infarction, and coronary death [24–26].

2. Association with cancer

2.1. Cancer types associated with alcohol drinking

As established by the IARC Monographs, consumption of alcoholic beverages is causally associated with cancers of the oral cavity, pharynx, larynx, oesophagus, colorectum, liver (hepatocellular carcinoma), and female breast in a dose-dependent manner [2]. Summary relative risks (RR) supporting these associations both for light and heavy drinking are indicated in Table 1. The relationship between alcohol consumption and cancer risk is monotonic and without a threshold (Fig. 2). Alcohol consumption accounts for about 3% and 10% of total cancers diagnosed in women and men, respectively [27]. In both genders, the alcohol-attributable fraction is high for upper aero-digestive tract (25–44%), liver (18–33%), and colorectal (4–17%) cancers, and in women for breast cancer (about 5%), with variation across EU countries related to different levels of exposure to alcohol [27]. Drinking patterns play an important role in modulating the relationship between alcohol and cancer risk. The strongest associations are observed for heavy drinking, in particular regular heavy drinking. Any reduction in alcohol consumption has a beneficial effect on reducing the risk of cancer.

2.1.1. Neoplasms of the upper digestive tract: oral cavity, pharynx, larynx and squamous-cell carcinoma of the oesophagus

Results from cohort studies and recent meta-analyses provide convincing evidence that the consumption of alcoholic beverages increases the risk of neoplasms of the upper digestive and respiratory tracts (UADT) even in the absence of smoking. Significant dose–response relationships are found with different

Table 1
Meta-analyses on alcohol consumption and cancer risk at different intakes.

Cancer	ICD-10 code	Reference	RR (95%CI) Light drinkers[#]	RR (95%CI) Heavy drinkers[#]
Oral cavity	C00–C13	Turati et al. [89]	1.17 (1.01–1.35)	4.64 (3.78–5.70)
Pharynx			1.23 (0.87–1.73)	6.62 (4.72–9.29)
OP cancers		Turati et al. [33]	2.55 (2.15–3.02)	5.40 (4.49–6.50)
Larynx	C32	Islami et al.[+] [31]	0.88 (0.71–1.08)	2.62 (2.13–3.23)
Oesophagus	C15	Tramacere et al. [90]	0.92 (0.78–1.09)	1.16 (0.92–1.46)
		Islami et al. [32]	1.32 (0.90–1.60)	3.35 (2.35–4.78)
Colorectal	C18–C21	Fedirko et al. [43]	1.21 (1.13–1.28)	1.52 (1.27–1.81)
Liver	C22	Corrao et al.[+] [48]	1.19 (1.12–1.27)	1.40 (1.25–1.56)
Female breast	C50	Bagnardi et al. [44]	1.05 (1.02–1.08)	
		Corrao et al.[+] [48]	1.25 (1.20–1.29)	1.55 (1.44–1.67)

ICD-10: International Classification of Diseases, 10th Revision [91].
[#] Light drinker (≤1drink/g or 12.5 g/day); heavy drinker (≥4 drinks/day or 50 g/day).
[+] Light drinker (≤25 g/day); heavy drinker (≥50 g/day).

metrics of exposure to alcohol such as level, frequency [28] and duration [29] of consumption, and for moderate intake in women [4,30,31]. Among non-smokers, reported RRs for oesophageal squamous-cell carcinoma and laryngeal cancer range from 0.74 (95%CI: 0.47–1.16) for light intakes to 3.09 (95%CI: 1.75–5.46) for high intakes [31,32]. Risks for oropharyngeal cancer are as high as 5.40 (95%CI: 4.49–6.50) [33]. The combined exposure to alcohol drinking and tobacco smoking results in a supra-multiplicative synergistic effect which enhances the risk of these neoplasms up to 14-fold, among heavy smokers and heavy drinkers (four or more drinks/day) [34,35] (Fig. 3).

There is evidence that the risk of UADT cancer decreases with time since drinking cessation, without however ever falling to that of lifetime abstainers. A recent meta-analysis reports an average 2% decreased risk of pharyngeal and laryngeal cancers per year of cessation [36]. A trend for decreased risk is suggested for laryngeal, oropharyngeal and oesophageal cancers among former drinkers. After at least 6 years of drinking cessation, odds ratios decreased to 1.24 (95%CI: 0.68–2.47) [37], 1.74 (95%CI: 0.77–3.92) [38], and 0.85 (95%CI: 0.78–0.92) for laryngeal, oropharyngeal and oesophageal cancers, respectively [39,40].

2.1.2. Neoplasms of the lower digestive tract: colorectum and liver

Results from cohort studies and recent meta-analyses provide overall evidence of a linear dose–response relationship between average alcohol consumption and cancers of the liver and colorectum. Summary effect estimates for colorectal cancer are about 11% (RR = 1.11; 95%CI: 0.90–1.38) at one drink/day (corresponding to 10–12 g of ethanol) and 40% (RR = 1.41; 95%CI: 1.16–1.72) at more than 4–5 drinks/day [41]. The risk is higher for drinkers with a family history of colorectal cancer (RR = 2.80; 95%CI: 2.00–3.91 at ≥30 g/d compared with non-drinkers with no family history) [42]. Overall, a slightly higher risk is reported for colon cancer (RR = 1.16, 95%CI: 0.97–1.39) than for rectal cancer (RR = 1.11, 95%CI: 0.97–1.29) at one drink/day [41], and the risk is greater in men (RR 1.24; 95%CI: 1.13–1.28) than in women (RR 1.08; 95%CI: 1.03–1.13) at less than 1 drink/day [43], compared to never drinkers. In both genders combined, dose–response analyses show RRs of 1.07 (95%CI: 1.04–1.10), 1.38 (95%CI: 1.28–1.50) and 1.82 (95%CI: 1.41–2.35) at 10, 50 and 100 g/day of alcohol consumption, respectively [43]. Associations of alcohol consumption with hepatocellular carcinoma are generally found at high intakes [44] with significant increased risks of about 30–40% at consumption levels >40 g/day [45–48]. An increased risk at low to moderate alcohol consumption is also reported [4,47,49].

2.1.3. Neoplasms of the female breast

A positive association between alcoholic beverage consumption and breast cancer risk is supported by more than 100 epidemiological studies [2]. The risk is increased by 8% for post-menopausal breast cancer, 9% for pre-menopausal breast cancer, and 10% for overall breast cancer [50], per 10 g/day of ethanol. While studies on binge drinking and cancer risk are still sparse, and a standardised measure of exposure is lacking, the available evidence shows that risk is increased between 33% (95%CI: 1.11–1.59, for monthly binge drinking) [51] and 55% (95%CI: 1.07–2.26, for weekly binge drinking) [52].

The degree of mammary development may determine a susceptibility window for exposure to alcohol consumption, which may be further defined by hormonal status or first full-term pregnancy [53]. However, at present few studies have investigated whether and to what extent the age at exposure increases cancer risk, and the evidence is generally limited. In the Nurses' Health Study (NHS) II, alcohol consumption during early adulthood was dose-dependently associated with an increased risk of proliferative benign breast disease, which may lead to invasive breast cancer later in life [54]. In contrast, a NHS prospective analysis reported similar breast cancer risks for categories of age at alcohol exposure of 18–40 years and >40 years (RRs = 1.21, 95%CI: 0.88–1.67 and 1.18, 95%CI: 1.03–1.34, respectively, for a daily intake of ≥20 g compared to none) [51]. A large Danish cohort of post-menopausal women also could not confirm a risk difference according to the age at which drinking was started [55].

2.2. Possible biological mechanisms

Alcoholic beverages mainly comprise ethanol and water and, in minor percentages, other volatile and non-volatile compounds. Ethanol is the most important carcinogen; moreover, the metabolism of ethanol activates various pro-carcinogens present, as well as inhaled or ingested, in alcoholic beverages. Regarding breast cancer, ethanol most likely acts as both a weak cumulative carcinogen and a tumour promoter of pre-existing breast cancer cells [56]. For cancers of the oral cavity, pharynx, larynx and oesophagus, the higher than multiplicative risk observed among drinkers and smokers is explained by the synergistic effect of carcinogens contained in tobacco smoke and in alcoholic beverages which leads to mucosal hyperproliferation [57–60].

The risk of digestive tract cancers is modulated by variants of the ethanol-metabolising enzymes, the alcohol and acetaldehyde dehydrogenases (ADH and ALDH). The *ADH1B* 47Arg allele is strongly associated with increased UADT cancer risk (RR = 3.47; 95%CI: 2.76–4.36 for the Arg/Arg genotype compared to the His/His genotype) [61]. The fast-metabolising *ADH1C*1* variant, which is more frequent in Caucasians [62], may increase the risk of head and neck cancer [63,64]. The *ALDH2* Lys487 allele promotes acetaldehyde accumulation and is associated with higher risk of oesophageal cancer [2].

Ethanol also disrupts folate metabolism regulated by methylenetetrahydrofolate reductase (MTHFR) [65]; an individual's

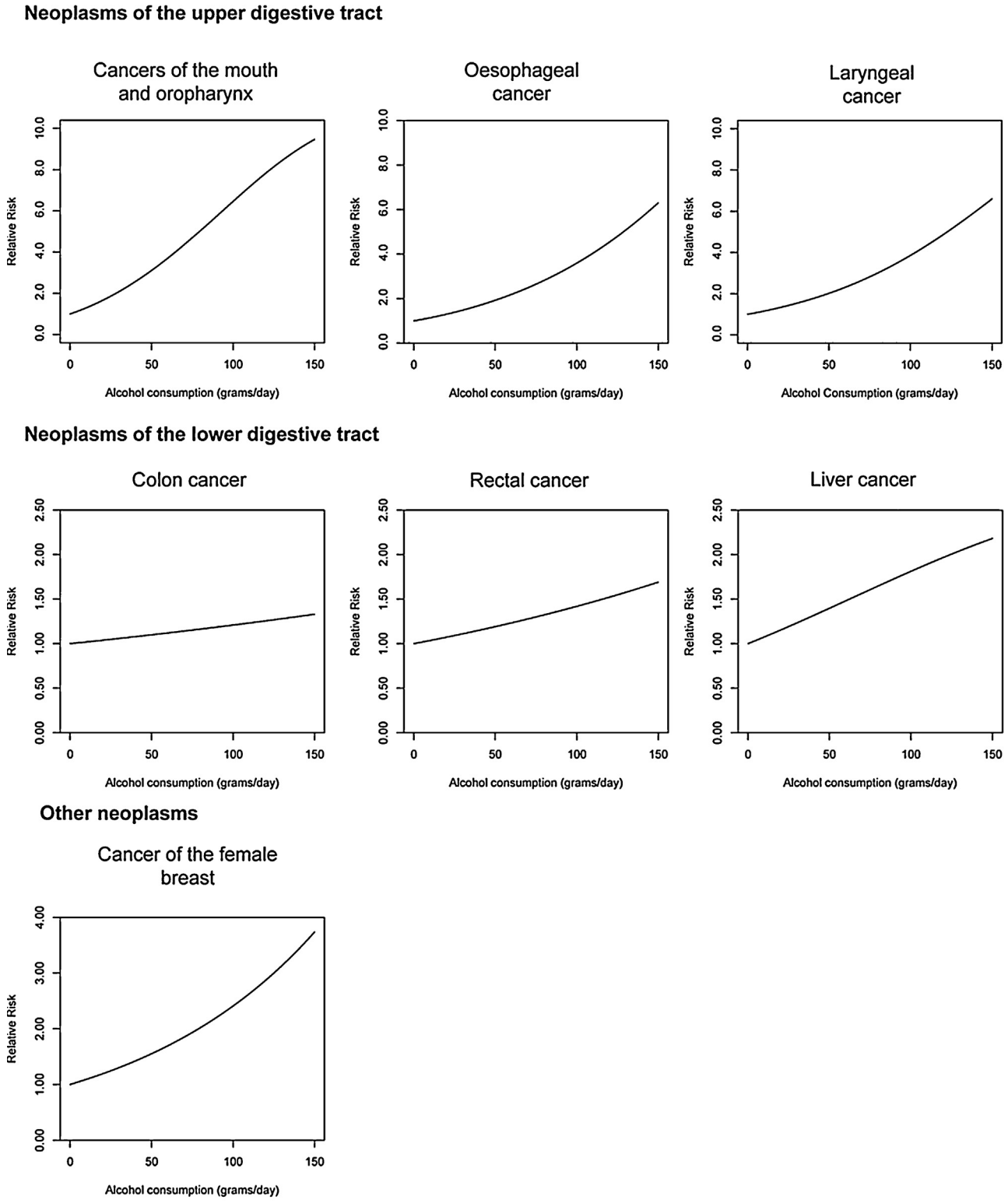

Fig. 2. Relationship between average daily alcohol consumption and relative risk of cancer. Plots of the relative risk functions for all cancers causally associated with alcohol consumption. The relationship between alcohol consumption and cancer risk is monotonic and without a threshold. From Corrao et al. [48] http://dx.doi.org/10.1016/j.ypmed.2003.11.027 PMID:15066364.

genotype for the C677T *MTHFR* variant modulates the effect of alcohol consumption on cancer risk. The CC or CT variants may increase colorectal cancer risk among alcohol drinkers (RR = 1.87; 95%CI: 1.29–2.71) [66]. The TT variant decreases MTHFR activity by 70% and appears to modulate risks of breast cancer, in association with low folate intake [67,68], and of oral cancer [69], at daily consumption of $\geq$2 drinks.

The alcohol-related increase in androgen and oestrogen levels [70] has been suggested as a key mechanism for breast cancer's development. Most studies observe overall a stronger association

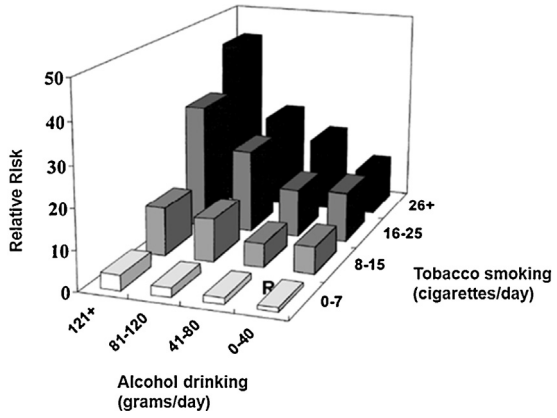

Fig. 3. Estimated relative risk (RR) for the interaction between tobacco smoking and alcohol drinking on cancers of the upper respiratory tract (reference category, risk = 1). Combined exposure to alcohol drinking and tobacco smoking increases the risk of upper digestive and respiratory tract neoplasms in a supra-multiplicative manner. From P. Boyle, P. Autier, H. Bartelink, et al. European Code Against Cancer and scientific justification: third version (2003) Annals of Oncology 2003, 14: 973–1005, by permission of Oxford University Press [7].

with the most common oestrogen-receptor-positive (ER+) and/or progesterone-receptor-positive (PR+) markers compared with ER− and/or PR− breast tumours, for the highest versus the lowest alcohol consumption group [71–73]. A meta-analysis showed that for each additional drink, breast cancer risk increases by 12% among ER+ subjects, by 11% among ER+PR+ subjects, by 15% among ER+PR− subjects, and by 7% for all ER− subjects, and no association was apparent with ER−/PR− or ER−/PR+ tumours when considered separately [74].

Other ethanol-mediated toxic effects associated with cancer development are cirrhosis of the liver and gastro-oesophageal reflux disease, which leads to hyperproliferation of the oesophageal mucosa. Also, ethanol-associated immune suppression may facilitate tumour cell spread [65].

3. Justification for recommendation

The consumption of alcoholic beverages is causally associated with cancers of the oral cavity, pharynx, larynx, oesophagus, liver, colorectum and female breast. Risk estimates of alcohol-related cancer incidence and mortality emphasise a dose-dependent relationship that does not vary by beverage type and does not show a threshold of intake, since the adverse effect is observed even at consumption of less than one alcoholic drink per day [12,75]. Ethanol carcinogenesis may not uniformly target tissues and may depend on drinking patterns and timing of exposure, as based on observed differences in cancer risk across organ sites.

Taking all these issues into account, the ECAC has developed the following recommendation:

"If you drink alcohol of any type, limit your intake. Not drinking alcohol is better for cancer prevention."

3.1. Alcohol-attributable burden of disease

Worldwide, alcohol consumption is the second leading risk factor after tobacco in terms of morbidity, and it accounts for a significant number of deaths, particularly in high-income countries. In Europe, alcohol is the third leading risk factor for disease and mortality after tobacco and high blood pressure [76]. Alcohol is causally associated with about 60 types of disease, including heart disease, stroke and vascular diseases, as well as liver cirrhosis and cancer. Fetal exposure to alcohol strongly increases the risk of birth defects and intellectual impairments. Alcohol-use disorders (e.g., acute alcohol intoxication, alcohol-dependence syndrome) account for a significant share of total morbidity, particularly among men (44.5%) [1]. Alcohol also contributes to death and disability through accidents and injuries, assault, violence, homicide and suicide.

In the EU in 2004, almost 95,000 men and more than 25,000 women, aged 15–64, died prematurely of alcohol-attributable causes. This means that one in seven male and one in 13 female premature deaths in this age category were caused by alcohol [76]. In men in 2004, approximately two in five deaths were due to liver cirrhosis, one in three to injuries, and one in five (15.9%) to cancer. In women, more than two thirds of alcohol-attributable deaths arose from liver cirrhosis and cancer (30.7%; the largest proportion of which, 21%, involves breast cancer), with cardiovascular disease other than ischaemic heart disease as a distant third cause.

Almost 90% of the burden of disease attributable to alcohol is caused by heavy drinking, both regular and irregular. This has important implications for prevention and alcohol policy: any measure which aims to successfully reduce alcohol-attributable harm has to involve cutting down regular and irregular heavy drinking occasions.

3.2. Public policies on alcohol taxation as measures of prevention

Negative health effects and social harm caused by detrimental alcohol consumption can be reduced through effective prevention strategies. In 1979, the World Health Assembly called upon World Health Organization (WHO) member states to develop and adopt appropriate legislation and measures to tackle alcohol misuse [77]. Such efforts culminated with the endorsement, in 2010, of the global strategy on the harmful use of alcohol [78] that supports ten target areas for national actions, including: health sector response, community actions, drink-driving policies, limitation of the availability of alcohol, action on marketing and pricing policies, reducing the negative consequences of intoxication and reducing the public health effect of illegally and informally produced alcohol. Based on four key criteria (namely effectiveness, affordability, efficiency and acceptability/feasibility), the WHO has more recently identified restricted access to retailed alcohol, limitation of alcohol advertising, and taxes on alcohol as the best-performing interventions to tackle harmful alcohol use [79]. Both the enforcement of drink-driving laws and brief advice for excessive drinkers are valuable interventions, although their efficiency in some settings may be less attractive.

In particular, alcohol prices – and consequently affordability – are a strong determinant of alcohol consumption and can be altered by using taxes or direct price controls, including minimum price policies [80]. However, public policies on alcohol taxation are not always homogeneous across the EU. Countries with stricter and more comprehensive alcohol policies generally have lower levels of alcohol consumption. Observational studies suggest that the effects of taxation would be larger for moderate than heavy drinkers [81], women [82], and young consumers [83]. On average, a 10% increase in the price of alcohol is correlated with a 4.4% decrease in consumption, with some variability depending on the type of alcoholic beverage [84]. Sadly, between 1996 and 2004 affordability has increased by 50% or more in Estonia, the United Kingdom, Czech Republic, Finland and Ireland, and by a smaller amount in Portugal, Spain, Denmark, Sweden, France, Austria, the Netherlands, Greece, Germany, Poland and Belgium–in particular for young people [85]. Time-series analyses in Canada (British Columbia) showed that a 10% increase in the minimum price for alcohol reduces the consumption of spirits by 6.8%, of wine by 8.9%, of alcopops (flavoured, often sweet, alcoholic beverages) by 13.9%, and of beer by 1.5% [86]. The most common

approach in European countries is based on a combination of excise duty and value-added taxes, which should account for potential effects of the type of beverage consumed. As an example, the introduction of a tax on alcopops in Germany simply shifted consumption from spirit-based to beer-based beverages [87].

4. Conclusion

Worldwide, alcohol consumption is the second leading risk factor in terms of morbidity, and it accounts for a significant number of deaths, particularly in high-income countries. In Europe, it has been estimated that about 10% (95%CI: 7–13%) of all cancer cases in men and 3% (95%CI: 1–5%) of all cancer cases in women are attributable to alcohol consumption [12]. There is strong evidence that people can reduce their risk of cancer by limiting or cutting their consumption of alcoholic drinks. Overall, in European populations the risk of cancer in men who consume less than two alcoholic drinks (less than 20 g of pure alcohol) per day and in women who consume less than one alcoholic drink (less than 10 g of pure alcohol) per day is 6% lower (hazard ratio = 0.94; 95%CI: 0.90–0.96) than that in people with higher alcohol intakes [88]. On average, reducing the consumption from four or more to one or less alcoholic drinks per day may reduce the risk of liver cancer by 21% [48], the risk of colorectal cancer by 31% [43], and the risk of female breast cancer by 30% [48]. The WHO have stated clearly that increasing price, reducing availability and banning advertising are the most effective policy measures that should be implemented at the European level in order to decrease the alcohol-related burden of disease.

European Code Against Cancer.:

EUROPEAN CODE AGAINST CANCER:

12 ways to reduce your cancer risk

1. Do not smoke. Do not use any form of tobacco
2. Make your home smoke free. Support smoke-free policies in your workplace
3. Take action to be a healthy body weight
4. Be physically active in everyday life. Limit the time you spend sitting
5. Have a healthy diet:
   - Eat plenty of whole grains, pulses, vegetables and fruits
   - Limit high-calorie foods (foods high in sugar or fat) and avoid sugary drinks
   - Avoid processed meat; limit red meat and foods high in salt
6. If you drink alcohol of any type, limit your intake. Not drinking alcohol is better for cancer prevention
7. Avoid too much sun, especially for children. Use sun protection. Do not use sunbeds
8. In the workplace, protect yourself against cancer-causing substances by following health and safety instructions
9. Find out if you are exposed to radiation from naturally high radon levels in your home; take action to reduce high radon levels
10. For women:
    - Breastfeeding reduces the mother's cancer risk. If you can, breastfeed your baby
    - Hormone replacement therapy (HRT) increases the risk of certain cancers. Limit use of HRT
11. Ensure your children take part in vaccination programmes for:
    - Hepatitis B (for newborns)
    - Human papillomavirus (HPV) (for girls)
12. Take part in organised cancer screening programmes for:
    - Bowel cancer (men and women)
    - Breast cancer (women)
    - Cervical cancer (women)

The European Code Against Cancer focuses on actions that individual citizens can take to help prevent cancer. Successful cancer prevention requires these individual actions to be supported by governmental policies and actions.

The resulting recommendation of the 4th edition of the ECAC targeted to individuals is to limit or cut the consumption of alcoholic beverages.

Conflict of interest

The authors declare no conflict of interest.

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